SCIENTIFIC ABSTRACT

Allogeneic bone marrow transplantation (allo-BMT) in multiple myeloma has a curative potential, however it also has higher rate of treatment related mortality than autotransplantation. Both increased early mortality and long-term disease free survival may be attributed to GVHD and the graft-versus-myeloma (GVM) effect, respectively. To decrease the early mortality from allogeneic transplantation, T-cell depletion has been applied. While decreasing the incidence of GVHD, problems such as early relapse, graft failure and EB-virus related lymphoma have emerged. At our institution patients with relapsed myeloma following allo-transplantation have achieved complete remission following infusion of donor leukocytes, however with development of GVHD and associated problems. We are now proposing to perform a similar procedure, however, with the added safety of TK-gene transduction of the donor lymphocytes to control any adverse effects. The presence of a marker gene in the infused lymphocytes will also allow us to study the role and kinetics of lymphocytes following infusion. Additionally, data suggest that the GVM effect may precede GVHD. The proposed plan of study will also investigate this question. The specific aims to be pursued are to study:

1) Safety of TK-transduced donor lymphocyte infusions.
2) Efficacy of ganciclovir in decreasing the clinical manifestations of severe acute and/or chronic GVHD.
3) Anti-myeloma effect of donor T-lymphocytes
4) Occurrence of bone marrow hypoplasia following transduced-lymphocyte infusions and the role of donor lymphocyte removal with ganciclovir on its prevention.

Patients with multiple myeloma undergoing allo-transplantation with T-cell depletion will be entered on this protocol if they show evidence of persistent disease at day 90 or measurable relapse. Donor peripheral blood lymphocytes will be cultured in IL-2 and CD3. Lymphocytes will be transduced with the Herpes Simplex Thymidine Kinase (TK) gene using the retroviral construct G1Tk1SvNa.7 and the transduced cells will be selected in G-418. They will be infused only if $\geq$ 85% of the cells are transduced with the gene as detected by a ganciclovir killing assay.

In the first three patients 1 x 10^6 lymphocytes/Kg will be infused and on day 21 ganciclovir will be given to remove the infused lymphocytes. If at day 42 a complete or partial response with continued reduction in the measurable disease is observed, no further intervention will be contemplated until disease plateau or progression. If a patient does not have at least a partial response on day 42, then the same number of transduced cells as during the first infusion will be given. However, cells will not be cleared unless patient develops GVHD.

If no response or no Grade III or IV GVHD is seen in the first patients then the dose of infused lymphocytes will be escalated for three patients at each of the subsequent dose levels: 0.5, 1.0, 2.0 and 5.0 x 10^7 lymphocytes/Kg. The treatment plan will be similar to that described above for first three patients. Six additional patients will be entered at the dose level at which the expected response is observed or a dose level below the dose with limiting toxicity. Patients will be studied for infusion related toxicity, development of GVHD and response to ganciclovir infusion, anti-myeloma response and its relation with GVHD and effect on hematopoiesis.